REMARKS

This timely filed Reply is responsive to the final Office Action mailed March 29, 2007 and is accompanied by a Request for Continued Examination. Claims 1-15 and 21 were pending at the time of the Office Action. Claims 16-20 and 22-33 were previously withdrawn pursuant to a Restriction Requirement. By this Reply, claims 1, 3 and 10 are amended and claims 34-39 are added. No new matter is presented.

Amendments to the Specification

Paragraph [0105] was amended to replace "nanostructed" with "nanostructured." As evident from the title of the reference to which the sentence containing the correction refers ("Surface-Enhanced Raman Spectroscopy Using Metallic Nanostructures"), this merely corrects a typographical error. Accordingly, no new matter is introduced.

Claim Amendments

Claims 1 and 10 were amended to recite SERS molecular probes (SMPs) "comprising at least one solid nanoparticle comprising an elemental metal, said nanoparticle having [[an]] a nanostructured outer surface that is surface-enhanced Raman spectroscopy (SERS) active." This language reflects the fact that the outer-surface of the nanoparticle is nanostructured in order to achieve the significant enhancement of the Raman signal that resulted in rejuvenation of the Raman technique, *see* Specification, paragraph [0016]. At the time the application was filed a "SERS-active surface" was understood to exhibit an enhancement of at least 10^6 or more, *see id.* The phrase SERS active is used throughout the specification, including paragraphs [0018] & [0100].

New claims 34-39 are drawn to nanoparticles with (i) a diameter from about 10 nanometers to 100 nanometers, (ii) an outer surface that provides a Raman enhancement of at least 10^6, and/or (iii) an outer surface that provides a Raman enhancement of at least 10^{10}. Support for these amendments can be found throughout the specification, including the following, (i) nanoparticle diameter – paragraph [0063], (ii) & (iii) Raman enhancement – paragraphs [0016]-[0017]. Accordingly, no new matter is introduced.

Prior Art Rejections Under 35 U.S.C. §102(b) and §103(a)

In the Office Action claims 1-4, 7-14 and 21 were rejected under 35 U.S.C. §102(b) as being anticipated by Dubertret *et al.* published as WO 02/18951 (hereinafter "Dubertret"), as evidenced by a chapter in a book by Lakowicz entitled "Principles of Fluorescence Spectroscopy", Second Edition, pgs. 25-61, 1999 (hereinafter "Lakowicz"). In the Office Action claims 5 and 6 were rejected under 35 U.S.C. §103(a) as being anticipated by Dubertret in view of U.S. Patent No. 6,417,340 issued to Mirkin *et al.* (hereinafter "Mirkin").

According to the Examiner:

> Regarding claims 1 and 9, Dubertret et al. teach an oligonucleotide-based molecular probe, the probe comprising:
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> at least one solid nanoparticle comprising an elemental metal, said nanoparticle having an outer surface component (Fig. 1B; page 5, lines 14-24; page 6, lines 1-15), and
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> at least one pin loop, said pin loop including a loop sequence complementary to at least one target sequence, a first stem attached to one end of said pin loop having at least one SERS active label attached thereto and a second stem attached to the other end of said pin loop and said nanoparticle, wherein said probe generates a stronger SERS signal upon irradiation with excitation radiation when not bound to said target sequence as compared to a SERS signal following

hybridization of said probe with said target sequence (Fig. 1B; page 4, lines 16-24; page 5, lines 14-24; page 6, lines 1-15). Since rhodamine 6G is a SERS label, the molecular beacon will inherently have stronger SERS signal in the closed form than in the open form).

Regarding claims 2 and 3, Dubertret et al. teach metal films and metal particles (page 3, lines 16-19).

Regarding claim 7, Dubertret et al. teach multiple fluorescent labels with different emission characteristics (page 11, lines 3, 4).

Regarding claim 8, Dubertret et al. teach Cu, AG or Au (page 9, lines 3-9).

Regarding claims 10 and 11, Dubertret et al. teach a spectrofluorometer comprising a light source and the molecular beacons (page 25, lines 18-24; page 26, lines 1-9).

Regarding claims 4, 12, 14 and 21, Dubertret et al. teach multiple beacons bound to a solid metal surface (page 20, lines 16-22), therefore they inherently teach multiple loops attached to a substrate.

Regarding claim 13, Dubertret et al. teach a spectrofluorometer (page 25, line 18). As evidenced by Lakowicz, every spectrofluorometer possesses a detection system which is either a photomultiplier (page 41, last two paragraphs; page 42-46; page 47, first paragraph), photodiode (page 47, second paragraph), avalanche diode (page 47, third paragraph) or a CCD detector (page 47, paragraphs 4-5).

Prior to addressing the cited references, Applicants review the invention as currently set forth in amended claim 1:

> 1. (Currently amended) A oligonucleotide-based surface-enhanced Raman spectroscopy molecular probe (SMP), comprising:

> at least one solid nanoparticle comprising an elemental metal, said nanoparticle having [[an]] a nanostructured outer surface that is surface-enhanced Raman spectroscopy (SERS) active, and
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> at least one pin loop, said pin loop including a loop sequence complementary to at least one target sequence, a first stem attached to one end of said pin loop having at least one SERS active label attached thereto and a second stem attached to the other end of said pin loop and said nanoparticle, wherein said probe generates a stronger SERS signal upon irradiation with excitation radiation when not bound to said target sequence as compared to a SERS signal following hybridization of said probe with said target sequence.

The claimed SMP includes at least one solid nanoparticle having a nanostructured outer surface that is SERS active. At the time the specification was filed, a surface was not considered SERS active unless it exhibited an enhancement of at least 10^6 compared to conventional Raman Spectroscopy, *see* Specification, paragraph [0016]. As evidenced by the specification and applicant VoDinh's publications cited in the specification, it was well known at the time the application was filed that Raman signal enhancements reaching this level required a nanostructured surface, *see* Specification, paragraph [0105] and references cited therein.

It is also well known that probes and indicators used in fluorescent spectroscopy are selected in order to minimize the Raman peaks, *see* Lakowicz, p. 39, paragraph bridging the first and second columns. This is because accurate fluorescent spectroscopy requires a fluorescent emission spectrum signal that overwhelms the Raman peak, *see id.* Because limiting the strength of the Raman signal is necessary to avoid distortions of the fluorescent emission spectrum, the fluorescent probe in Dubertret would not be nanostructured in a manner to make the nanoparticle SERS active as required by the claimed invention.

This is evidenced by the fact that Dubetret discloses that the preferred particle size (diameter) for Dubertret's nanoparticles is about 1.4 nanometers, *see* Dubertret, p. 6, ln. 12. It was, and is, well known that when SERS active surfaces are formed using nanoparticles, the nanoparticles must be significantly larger than 1.4 nanometers, generally on the order of 100 nanometers, *see* Specification, paragraph [0045]. It is equally well known that nanoparticles on the order to 1.4 nanometers would not result in a SERS active surface.

Based on the knowledge in the art, it would have been clear that Dubertret's disclosure did not place the currently claimed invention, which deals with SERS spectroscopy not fluorescent spectroscopy, in the possession of the public. This is evident in that Dubertret's disclosure must be construed in the context of a fluorescent spectroscopy reference. In this context, it is clear that Dubertret does not disclose or suggest particles in the proper range and does not disclosure or suggest a nanostructured surface, as the term is used by those skilled in the art of SERS spectroscopy. Clearly, Dubertret does not disclose the claimed nanostructured surface which is necessary to provide the claimed SERS active surface.

Applicants wish to review a portion of the law relevant for making a rejection under 35 U.S.C. § 102. In order for a claim to be anticipated by a reference disclosing a range or variety of ranges, the reference must disclose the range with "sufficient specificity," *see* MPEP 2131.03.II. For example, in *Atofina v. Great Lakes Chem. Corp*, 441 F.3d 991, 999 (Fed. Cir. 2006), the court held that a reference temperature range of 100-500 degrees Celsius did not describe the claimed range of 330 – 450 degrees Celsius with sufficient specificity to be anticipatory. Even more significantly, the court noted that although there was an overlap between the claimed range and the reference's preferred range (150-350 degrees Celsius), **the overlap was not sufficient for anticipation**. *see* MPEP 2131.03.II. The MPEP suggests looking to the preferred embodiments to determine which compounds [nanoparticle diameter in our case] are anticipated, *see id.*

Dubertret discloses that the preferred particle diameters are on the order of 0.8 and 1.4 nanometers. While this particle size is sufficient to quench a fluorescent signal, it is not sufficient to produce a SERS active surface. It is well known in the art of SERS spectroscopy that particles less than 2 nanometers, are simply too small to provide a SERS active surface. Thus, Dubertret's disclosure does not disclose the claimed invention with sufficient specificity because the claimed invention requires a *SERS active surface*, which cannot be produced using the preferred nanoparticles described in Dubertret.

In conclusion, it is clear that Dubertret does not disclose or suggest the claimed SMP with a nanostructure surface that is SERS active, because Dubertret does not disclose or suggest the necessary nanostrucuturing and does not disclose or suggest the particle size necessary to achieve a SERS active surface with sufficient specificity. Accordingly, Applicants respectfully request withdrawal of the current rejection.

New Claims

New claims 34-39 are drawn to aspects of the claimed invention that further distinguish the pending claims from those of the cited references. Each of the elements in these claims is either not disclosed at all by Dubertret or not disclosed by Dubertret with "sufficient specificity," as required by the MPEP, *see* MPEP 2131.03.II.

Conclusion

Applicants have made every effort to present claims which distinguish over the cited art, and it is believed that all claims are in condition for allowance. However, Applicants invite the Examiner to call the undersigned if it is believed that a telephonic interview (direct line: 561-671-3624) would expedite the prosecution of the application to an allowance. The

Commissioner is hereby authorized to charge the $395 fee for a Request for Continued Examination to Deposit Account No. 50-0951. No additional fees are believed to be due; however, the Commissioner for Patents is hereby authorized to charge any deficiency or credit an surplus to Deposit Account No. 50-0951.

Respectfully submitted,

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